REMARKS

The Office Action has rejected claims 26 and 27 are rejected under 35 U.S.C. §112. In light of the amendments above and the arguments below, Applicant respectfully request reconsideration.

35 U.S.C. §112, Second Paragraph Rejections

Claims 26 and 26 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner has noted the phrase "a substance as a positive strand RNA antiviral agent" in claims 26 and 27. The Examiner questions "whether the substance is considered as a 'positive strand RNA' or as an anti-viral agent against 'positive strand RNA virus.'" Applicant means for the phrase to indicate an antiviral agent against positive strand RNA virus. Applicant has amended claims 26 and 27 to make this clear.

35 U.S.C. §112, First Paragraph Rejections

Claims 26 and 27 remain rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner notes that the clones encompass a genus of numerous different $\triangle 9$ fatty acid desaturase enzymes and asserts that "the genus is highly variant because a significant number of structural differences between genus members is permitted."

Applicants note new claims 30 and 31 are drawn to the yeast *OLE1* desaturase enzyme.

Applicants point out that the Examiner is confusing sequence variation and functional variation. The fact that structural differences may exist between genus members is inconsequential to the present invention. Applicants have shown that $\triangle 9$ fatty acid desaturase enzymes are appropriate for the present invention. Applicants are not required to have possession of all the $\triangle 9$ fatty acid desaturase enzymes that are encompassed by the claims. Applicants are required to describe the invention.

The art understands the nomenclature "$\triangle 9$ fatty acid desaturase enzymes" and what enzymes would or would not fit within this category.

The Examiner has noted that "the biological function of various mammalian homologs of yeast $\triangle 9$ fatty acid desaturase enzyme was unpredictable from the protein function of yeast $\triangle 9$ fatty acid desaturase enzyme at the time of the invention." Applicants respond that the native biological function of these homologs, other than their role as a $\triangle 9$ fatty acid desaturse, is not important or necessary to understand for one to have possession of the present invention. Applicants have presented an assay, a

method of evaluating a substance as a positive strand RNA antiviral agent, and all that is necessary for this assay is that one expose a test substance to a yeast or mammalian △9 fatty acid desaturase enzyme. The biochemical properties of these enzymes within their host organisms is not important to the enzyme. Only the function of the enzyme is important.

In contrast to the Examiner's comments, mammalian homologues of OLE1 were well known at the time of the invention, as shown e.g. by Stukey et al. 1990 (Exhibit A) and references therein. Mouse and rat △9 fatty acid desaturases, e.g., were both sequenced at the DNA level many years prior to the invention (Thiede et al., 1986; Ntambi et al., 1988). Moreover, mammalian △9 fatty acid desaturases were already known to efficiently function in yeast as a replacement for the normally essential yeast OLE1 gene, and extensive regions of amino acid sequence homology between mammalian and yeast OLE1 homologues were known (Stukey et al. 1990).

Claims 26 and 27 are rejected under 35 U.S.C. §112, first paragraph, as failing the enablement requirement. Applicants have presented Exhibits A and D in previous responses and argued that there is a universal dependence of RNA replication on expanded, rearranged membranes, on the synthesis and physical characteristics of these membranes, and on positive strand RNA viruses.

The Examiner is correct that Applicants have noted that △9 fatty acid desaturase enzymes convert SFAs to UFAs and positive strand RNA replication is strongly dependent on UFA levels and that modulating composition of membranes helps to identify useful antiviral agents. The Examiner does not find this persuasive because the Examiner finds that "different OLE1 proteins could have different biological functions and there is no evidence of record that a substance effecting a decrease in stability or inhibition of various *OLE1* proteins would be indicative of said substance having an antiviral therapy agent." (Office Action, page 5.)

These comments ignore substantial evidence of record that OLE1 homologs from yeast, mammals, etc. have equivalent biological function and are functionally interchangeable in providing essential △9 fatty acid desaturase functions that are absolutely required for cell growth (e.g., Stukey et al. 1990, Exhibit A). Moreover, these comments ignore that the application specifically claims △9 fatty acid desaturases, i.e., enzymes that by definition share the common biosynthetic function of modifying fatty acids by insertion of a double bond at a specific position. Using genetic and biochemical experiments including specific mutations, fatty acid feeding experiments, etc., the application clearly teaches that the partial or total inhibition of this △9 fatty acid

desaturase activity, the defining characteristic of the gene class, is inhibitory to viral RNA replication.

Any hypothetical possibility that such enzymes might have other functions is irrelevant, since the application shows that the inhibitory effect on viral RNA replication of partial inhibition of OLE1 function or total deletion of the OLE1 gene are completely reversible by feeding UFAs with the relevant double bond. Thus, the $\triangle$9 fatty acid desaturase activity is the sole contribution of the gene to RNA replication and, as long as the UFA product of this activity is provided, the gene and its encoded protein are completely dispensable for RNA replication.

Earlier on page 5, the Examiner argues that:

> "there is no evidence of record that shows a correlation between a decrease in stability or inhibition of activity of various OLE1 proteins and an antiviral therapy. There is a possibility that a feedback regulation of UFAs can regulate the activity of delta9 desaturase enzyme, the UFAs levels may be regulated by mechanism other than delta9 desaturase enzyme, or some other enzyme can compensate the activity or instability of the delta9 desaturase enzyme such that a decrease in the stability or inhibition of activity of delta9 desaturase enzyme does not result in any antiviral activity."

Regarding the hypothetical possibility that " a feedback regulation of UFAs can regulate the activity of delta9 desaturase enzyme," any theoretical increase in $\triangle$9 fatty acid desaturase activity mediated by reduced UFA level could only affect the level of activity or dosage required for a substance acting on the stability or activity of the enzyme, but does not affect or challenge the fundamental nature of the inventions claimed. Moreover, the application makes clear that only partial inhibition of $\triangle$9 fatty acid desaturase activity is actually required to inhibit viral RNA replication. Therefore, that total inhibition is not required.

Regarding the hypothetical possibility that " the UFAs levels may be regulated by mechanism other than delta9 desaturase enzyme, or some other enzyme can compensate the activity or instability of the delta9 desaturase enzyme such that a decrease in the stability or inhibition of activity of delta9 desaturase enzyme does not result in any antiviral activity," prior results, well-established at the time of the invention, show this to be untenable. In both mammals and yeast, it was well established that synthesis of all UFAs proceeds through the action of $\triangle$9 fatty acid desaturase as the first step (Stukey et al., 1990 and references therein). Thus, inhibition of $\triangle$9 fatty acid desaturase stability or activity blocks any cell access to UFAs.

Summary

Applicants have amended the claims in this application or provided arguments to respond to all of the Examiner's rejections. Accordingly, Applicants respectfully request the Examiner to reconsider said rejections and to issue a Notice of Allowance in the claims currently under consideration.

RCE

Applicants have enclosed a Request for Continued Examination.

Fees

A petition for a three month extension of time accompanies this response so that the response is timely filed. No other extension of time is believed due, but should any additional extension be due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the extension fee to Deposit Account No. 17-0055. Applicants also authorize payment of the fee for filing a Request for Continued Examination is also included. No additional fees are believed due; however, if any fees are due, in this or any subsequent response, please charge Deposit Account 17-0055.

Respectfully submitted,

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